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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/464,795	12/16/99	ZHANG	N PXE-007.US

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EXAMINER	
SHUKLA,R	
ART UNIT	**PAPER NUMBER**
1632	11

DATE MAILED: 09/13/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/464,795	Applicant(s) ZHANG ET AL.
	Examiner Ram Shukla	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38,40,41,43,45,46,49 and 65-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,40,41,43,45,46,49 and 65-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12-16-99* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Amendment/response filed 6-25-01 has been entered.

2. Claims 39, 42, 44, 47, 48, 50, and 69-79 have been canceled.

3. Amendments to claims 38, 40, 41, 43, 45, 46, 49, and 65-68 have been entered.

4. Claims 38, 40, 41, 43, 45, 46, 49, and 65-68 are pending and under consideration.

Information Disclosure Statement

5. The information disclosure statement filed 6-25-01 fails to comply with 37 CFR 1.97(c) because it lacks a statement as specified in 37 CFR 1.97(e). It has been placed in the application file, but the information referred to therein has not been considered.

6. The information disclosure statement filed 6-25-01 fails to comply with 37 CFR 1.97(c) because it lacks the fee set forth in 37 CFR 1.17(p). It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

8. The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 38 and 65-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record set forth in the previous office action of 2-1-01.

It is noted that the amendment of claims to recite transgenic mouse does not obviate the rejection set forth in the previous office action and the grounds of

rejection and issues raised remain the same since the specification did not describe the structure and characteristic features of a transgenic mouse.

Response to Arguments

Applicant's arguments filed 6-25-01 have been fully considered but they are not persuasive. Applicants have argued that the specification discloses mouse control elements, methods of generating reporter constructs, that methods of generating and screening transgenic mice are known in the art and are described in the specification and that evaluation of expression mediated by the selected control elements of the present invention is also disclosed in the specification. However, the issue is not the method of making the transgenic mice, rather the issue is the descripiton of the transgenic mice and the specification does not teach what was the structure and identifying characteristic features of the claimed transgenic mouse. As noted in the previous office action, due to the unpredictability of the site of integration of the transgene in the genome, one may not know whether viable transgenic mice would have been produced, or if any transgenic mice are produced, one can not predict what would be their structure and identifying characteristic features.

Accordingly, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the huge genera recited in the claims at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera of the invention.

10. Claims 38, 40, 41, 43, 45, 46, 49, and 65-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record set forth in the previous office action of 2-1-01 and discussed below.

It is noted that the amendment of claims to recite transgenic mouse does not obviate the rejection set forth in the previous office action, while obviates some grounds of rejection and issues, pertaining to the making and using of any and all transgenic non-human animals, raised in the previous office action, following issues still remain and therefore, the claimed invention is not enabled, as discussed below.

Introduction of foreign DNA into fertilized oocyte , for example by micro injection, may result in random integration of the exogenous DNA into host chromosomal DNA which in turn may have major consequences on the expression of the transgene, therefore the production of transgene in all the non-human mammals species will be highly variable and unpredictable. While it is realized that making of a transgenic mouse has been more perfected over the years, making of transgenic mouse with a certain phenotype is not predictable, as noted below by Cameron et al, even because it is uncertain whether an artisan can produce a transgenic mouse of same phenotypes a second time using same expression construct.

" Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or the complete absence of expression, as well as less common problems, such as leaky expression in nontargeted tissues. A feature common to many transgenic experiments is the unpredictable transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy- number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene" (see page 256, section 4 on transgene regulation and expression in Cameron ER. Molecular Biotechnology 7:253-265, 1997).

Furthermore, Cui et al (Cui C et al. Transgenic Research 3:182-194, 1994) reviewing the state of the art of reporter genes in transgenic mice noted that when a lacZ construct was introduced in ES cells by electroporation and the resultant ES cells were injected in to blastocysts and whole embryos were tested for lacZ expression, each strain manifested a unique pattern of transgene expression indicating that the expression of the transgene is dependent on the site of

integration (see last paragraph in column 1 on page 184). It is noted that in the instant case the transgenic animals comprise more that one expression construct, and when the expression of one construct is not predictable, it is not clear how can the expression of multiple expression vectors be predicted. Yet another unpredictability of making transgenic animals with reporter genes has been the unpredictability whether the reporter gene would be expressed post-natally, even if the reporter gene was expressed at the embryonic stage. Again Cui et al noted that that the same promoter that expressed reporter gene lacZ in embryo did not direct expression in adult (see column 2 on page 186). While Cui et al used the example of lacZ, based on the prior art and the teachings of the specification, it is not clear whether the reporter genes of the claimed invention would have shown same level of expression in the embryos and adult animals.

As noted in the previous office action, reegarding the method claims (claims 40, 41, 43, 45, and 46), it is noted that if the making of the transgenic mouse was unpredictable, it is not clear how would an artisan know how to use these transgenic mice in claimed methods without knowing the characteristics of the transgenic animals. In addition to the making of the transgenic animals encompassed by the claimed invention, the specification fails to provide sufficient guidance as to how an artisan would have used the claimed transgenic animals in the claimed methods. It is noted that the transgenic may not be expressed to the same extent in all the cell types or tissues or sites in the body. Alternatively, different tissues of the transgenic animal may express the transgene to different levels. Additionally, in the claimed method first an analyte has to be administered to the transgenic animal which has to reach the control element of the transgene in the nucleus of a cell after it has entered a cell via a receptor or any other method and an analyte may affect more than one stress gene and the extent of effect may not be distinguishable from each other. The specification in pages 35-41 has disclosed an extensive list of gene whose expression is altered under stress and therefore, their control element may be used in the expression constructs in any combination of at least two control elements. However, the specification does not provide any guidance as to whether the activity of all these elements would have

been affected by an analyte in vivo when the promoter is inserted in the genome not at its natural site. It is reiterated that the specification does not dislcose a working example of making and using a transgenic mouse.

Response to Arguments

Applicant's arguments filed 6-25-01 have been fully considered but they are not persuasive.It is noted that in response to applicants amendments, issues raised in the previous office action pertaining to any and all transgenic animals have been withdrawn. However, the rejection pertaining to the transgenic mouse and methods of use is maintained and applicants' arguments are not persuasive.

Applicants', in their arguments, have cited two US Patents 5,650,135 and 6217847 co-owned by the Contag et al. It is noted that the teachings of US patent 5,650,135 were analyzed and discussed in the previous office action (see pages 8 and 9) and therefore would not be repeated here. Regarding patent 6,217,847, it is noted that the transgenic mouse disclosed in this patent does not address the issues raised in the office action because the instantly claimed transgenic mouse recites a panel of expression cassettes whereas the transgenic mouse of 6,217,847 expresses only one expression cassette. Therefore, the issues of unpredictability raised in the instant case can not be addressed by the teachings of 6,217,847.

Applicants argue that not every species encompassed by the claims need to be disclosed and have cited In re Angstadt; Cook; Horton v Stevens, etc in support. Applicants further argue that to facilitate prosecution they have limited the claimed invention to transgenic mice. However, as noted above, the specification is not enabling for making and using of the claimed invention as pertaining to a transgenic mouse because the method of making a transgenic mouse is unpredictable and an artisan would not have been able to use the claimed transgenic mice as claimed.

In summary, although the of the art of making of transgenic mice is highly unpredictable and unless a transgenic mouse has been produced, one can not predict what will the characteristics of the transgenic mouse comprising a given

panel of expression constructs and therefore, an artisan would not know how to use the claimed transgenic mouse in claimed methods.

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c) and a copy of all the pending/under consideration claims. For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Ram R. Shukla, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER